

# PATENT SPECIFICATION

(11) 1 442 951

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- (21) Application No. 49511/74 (22) Filed 15 Nov. 1974  
 (31) Convention Application No. 2 357 503  
 (32) Filed 17 Nov. 1973 in  
 (33) Germany (DT)  
 (44) Complete Specification published 21 July 1976  
 (51) INT CL<sup>2</sup> A61J 3/00  
 (52) Index at acceptance  
 A5B 232 23X 23Y 248 24Y 26Y 273 27X 27Y 293 29Y  
 303 351 35Y 382 38Y 421 42Y 451 45Y 482 48Y  
 503 50Y 550 55Y 576 57Y 616 61Y 764  
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## (54) PRODUCTION OF SOLID PREPARATIONS CONTAINING CARBOCHROMENE HYDROCHLORIDE

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 (Main)-Fechenheim, Germany, a body corporate organised under the laws of Germany,  
 do hereby declare the invention for which we  
 pray that a patent may be granted to us,  
 and the method by which it is to be performed,  
 to be particularly described in and by the  
 following statement:—  
 This invention relates to the production of  
 solid preparations containing carbochromene  
 hydrochloride. Medicinal preparations as just  
 mentioned are at present produced either as  
 soft gelatin capsules or as dragées. The soft  
 gelatin capsules contain an oily suspension of  
 the active compound (i.e. carbochromene  
 hydrochloride) and are found to be unstable  
 in tests at elevated temperature, as too are  
 dragées containing carbochromene hydro-  
 chloride. This instability can be attributed to  
 the active compound being gradually decom-  
 posed hydrolytically under the influence of  
 moisture and elevated temperature. This has  
 had the consequence that when, for example,  
 the previously known preparations containing  
 carbochromene hydrochloride have had to be  
 despatched for use in the tropics, it has been  
 necessary to take quite exceptional precautions  
 in packing them, to prevent the active com-  
 pound being damaged by hydrolysis.  
 It has also been a disadvantage that a  
 considerable technical effort has been required  
 to protect the personnel operating the pro-  
 cessing equipment used, since carbochromene  
 hydrochloride, when it acts externally, has  
 skin-irritant properties which lead to certain  
 allergies. Thus, when the dragées have been  
 produced by granulating a starting material  
 made moist with alcohol, special measures  
 have been necessary for protection against dust  
 and explosion and for preventing contamina-  
 tion of the environment.

It may be mentioned here that, upon the  
 administration of the forms of carbochromene  
 hydrochloride which have hitherto been used  
 for peroral administration, the adsorption of  
 the active compound has taken place in the  
 upper and middle portions of the small  
 intestine.

Accordingly, there has been a need for a  
 process by which carbochromene hydrochloride  
 can be processed in a simple manner to pro-  
 vide solid preparations which remain stable  
 even under the influence of moisture and  
 warmth and which have optimal properties for  
 therapy.

According to the present invention, we pro-  
 vide a process for the production of a solid  
 preparation containing carbochromene hydro-  
 chloride, wherein carbochromene hydrochloride  
 together with based on the weight of the carbo-  
 chromene hydrochloride, 1—30% by weight  
 of filler, 1—20% by weight of swelling and  
 disintegrating agent, 1—10% by weight of  
 flowing and loosening agent, and 10—50%  
 by weight of melting aid are submitted to  
 heating and to intermixing at a temperature  
 in the softening range or melting range of  
 the melting aid, until granules are formed  
 therefrom.

In a process according to the invention, we  
 prefer to use, based on the weight of the  
 carbochromene hydrochloride, 2—20% by  
 weight of filler and/or 2—10% by weight of  
 swelling and disintegrating agent and/or 2—  
 8% by weight of flowing and loosening agent  
 and/or 15—30% by weight of melting aid.

The granules initially formed may if desired  
 be broken down, with a view to their being  
 administered in this form or processed into  
 solid forms for peroral administration, for  
 example capsules, tablets or dragées. The  
 breaking down of the granules may appro-  
 priately be carried out while the granules are  
 still in a plastic condition. The granules can

5 still be warm, or can still be cooling, or can  
have already cooled. In this breaking down,  
individual granule particles themselves are not  
broken, but larger bodies comprising a number  
10 of granule particles agglomerated with one  
another or adhering to one another at their  
points of contact are disintegrated to give  
individual granule particles. This breaking  
down may for example be effected on vibrating  
15 or oscillating sieves. If desired, a classification  
(according to particle size, that is) can follow  
this breaking down, or can be performed  
concurrently therewith. However, this classifica-  
tion is not necessary in most cases inasmuch  
as the individual granule particles resulting  
from the breaking down are mostly of a  
sufficiently uniform size.

20 The breaking down of the granules initially  
formed is not necessary if care is taken to  
ensure that granule particles do not agglom-  
erate to form larger bodies. This can be  
achieved, for example, by judicious termina-  
tion of the mixing operation and/or the supply  
of heat.

25 The granules produced can be utilised in  
solid form for the peroral administration of  
carbochromene hydrochloride either as pro-  
duced or, if desired, after breaking down and  
classification of granule agglomerates.

30 It is also possible, however, for the granules  
to be processed into other solid forms for  
administration; for example, they may be  
made into capsules, tablets or *dragées*. For  
this purpose it is generally appropriate addi-  
35 tionally to admix with the granules 1—10%  
by weight (preferably 2—5% by weight) of  
a swelling and disintegrating agent, and/or  
1—15% by weight (preferably 2—10% by  
weight) of a flowing and loosening agent and/  
40 or mould release agent and lubricant. The  
resulting mixture may, for example, be put  
into capsules or made into tablets, which may,  
for example, be single-layer tablets, multi-  
layer tablets or dry-coated tablets, or again  
45 made into cores for film-coated or sugar-  
coated tablets.

50 In a process according to the invention it  
is not necessary that the carbochromene hydro-  
chloride, filler, swelling and disintegrating  
agent, flowing and loosening agent and melt-  
ing aid should be heated to a temperature  
so high that the melting aid, or even the  
entire mixture, has completely melted. Thus  
in accordance with the invention, the com-  
55 position has only to be heated, while being  
mixed, until the melting aid (this being a  
material which does not have a sharp melting  
point, but has a softening range or melting  
range) reaches its softening range or melting  
60 range.

65 The melting aid used in accordance with  
the invention serves the purposes of enabling  
or facilitating the formation of the granules,  
and of controlling the hydrophilic-lipophilic  
properties of the preparation which is finally

produced. The melting aids which we con-  
template generally have melting ranges or  
softening ranges between 40°C and 100°C,  
preferably between 55°C and 85°C. Ex-  
70 amples of suitable melting aids are: hydro-  
genated oils, e.g. hydrogenated castor oil,  
hydrogenated coconut oil, hydrogenated  
groundnut oil; esters, especially mono-, di-  
and tri-glycerides of fatty acids, e.g. glyceryl  
75 mono-stearate/palmitate, glyceryl tri-stearate/  
palmitate, self-emulsifying glyceryl mono/di-  
stearate, glyceryl mono/di/tri-stearate/pal-  
mitate, and esters of purified montan wax  
acids, for instance Hoechst Wax E ("Hoechst  
is a registered Trade Mark"); higher fatty  
80 acids or wax acids, e.g. stearic acid, palmitic  
acid, behenic acid, myristic acid and purified  
montan wax acids, for instance Hoechst Wax  
S; higher fatty alcohols, e.g. lauryl alcohol, 12-  
hydroxystearyl alcohol, cetyl alcohol, stearyl  
85 alcohol, myristyl alcohol, myricyl alcohol,  
arachidyl alcohol, carnaubyl alcohol and ceryl  
alcohol; and natural, partly synthetic and  
wholly synthetic waxes, e.g. beeswax, carnauba  
wax, paraffin wax, vaseline wax, ozokerite,  
ceresine, spermaceti, solid polyethylene gly-  
cols, and polyethylene having a low softening  
point, for example Hoechst Wax PA 250.

The following are preferably used as melt-  
95 ing aids: purified montan wax acid esters,  
e.g. Hoechst Wax E, purified montan wax  
acids, e.g. Hoechst Wax S, carnauba wax,  
hydrogenated castor oil, glyceryl mono/di/tri-  
stearate/palmitate, and polyethylene glycols  
100 having average molecular weight of 4,000—  
20,000.

The fillers used in accordance with the  
invention serve to increase the mass of the  
preparation and in certain cases they also make  
it possible to influence the dissolving charac-  
105 teristics and the pH and ionisation charac-  
teristics of the preparations. Examples of suitable  
fillers are: calcium hydrogen phosphate di-  
hydrate, calcium tri-phosphate, calcium sul-  
phate dihydrate, sodium carbonate, sodium  
bicarbonate, calcium carbonate, magnesium  
carbonate, ammonium chloride, citric acid,  
tartaric acid, lactose, sucrose, mannitol, kaolin,  
diatomaceous earth, cellulose and micro-  
110 crystalline cellulose. Calcium hydrogen phos-  
phate dihydrate, calcium sulphate dihydrate  
or lactose are preferably used as fillers.

The swelling and disintegrating agents used  
serve the purpose of controlling the disintegra-  
120 tion characteristics of the preparation. Ex-  
amples of suitable swelling and disintegrating  
agents are: starch (rice starch, maize starch,  
potato starch and various other kinds), sodium  
amylpectin glycollate (ultra-amylpectin),  
125 methylcelluloses, isopropylmethylcelluloses,  
methylhydroxyethylcelluloses, hydroxypropyl-  
celluloses, hydroxyethylcelluloses, hydroxy-  
propylmethylcelluloses, carboxymethylcellu-  
loses and salts and esters thereof, alginic acids  
130 and salts and esters thereof, polyacrylic acids

and salts and esters thereof, guar gum, carageen, carboxymethyl dextrans and sodium carboxymethyl starch. The agents which we prefer, however, are: starch, sodium amylopectin glycollate (ultra-amylopectin) and methylhydroxyethylcelluloses and sodium carboxymethylcelluloses having a viscosity of 500—1,500 cP, sodium carboxymethyl-starch and crosslinked polyvinylpyrrolidone.

The flowing and loosening agents used serve the purposes of controlling the mixing behaviour of the composition during the granule-forming process, and of controlling the porosity of the granules. Examples of suitable flowing and loosening agents are: colloiddally dispersed silicic acid, e.g. Aerosil 200 ("Aerosil" is a registered Trade Mark), colloiddally dispersed hydrophobic silicic acid, e.g. Aerosil R 972, and amorphous silicic acids, e.g. Syloid (various grades: "Syloid" is a registered Trade Mark). Colloiddally dispersed (optionally hydrophobic) silicic acid is a preferred agent.

Mould release agents and/or lubricants may optionally be used in a process according to the present invention; they may if necessary be used together with flowing and loosening agents of the kind already mentioned, in the further processing of the resulting granules. Examples of suitable mould release agents and lubricants are magnesium stearate, calcium stearate, zinc stearate, aluminium stearate, calcium behenate, talc and silicone oil. Magnesium stearate is preferably used as the mould release agent and lubricant.

The active compound carbochromene hydrochloride can also be combined with other pharmaceutically active substances, for example with digoxin,  $\alpha$ -methyl digoxin, Cymarin, Nifenalol, Hydroxyzin, nicotinic acid and salts and esters thereof, clofibrac acid and salts and esters thereof, xanthines and xanthine derivatives, pyridine-3-carbinol, dihydroergotamine tartrate, potassium chloride, Rauwolfia alkaloids, thiabutazide, Clofenamid, Hydralazin theophyllinate, phenobarbital, Prenylamin, Dipyrindamol, nitroglycerin, pentaerythritol tetranitrate and chlorodiazepoxide hydrochloride.

Substances approved by Public Health authorities are used as auxiliaries, that is to say as fillers, swelling and disintegrating agents, flowing and loosening agents, melting aids and mould release agents and lubricants.

Not merely a single melting aid, but a mixture of two or more melting aids, is generally used. In the case of the other groups of auxiliary substances, it is also possible to use mixtures, that is to say, for example, a mixture of various swelling and disintegrating agents or a mixture of various flowing and loosening agents.

The percentages quoted relate to the total mixture present in each case.

The availability of the active compound in

the gastrointestinal tract can be controlled in a manner which is optimal for therapy by means of a suitable qualitative and quantitative selection in the hydrophilic-lipophilic composition of the melting aid, together with a suitable qualitative and quantitative selection of the fillers, swelling and disintegrating agents, flowing and loosening agents, and mould release agents and lubricants. If, for example, a melting aid or a mixture of melting aids with predominantly lipophilic properties is used, the liberation of the active compound is delayed, while when using a melting aid or a mixture of melting aids with predominantly hydrophilic properties, the release of the active compound takes place more quickly.

The porosity of the resulting granules can be controlled, and the penetration of liquid can be accelerated or delayed, by means of a suitable qualitative and quantitative selection of the loosening agents.

By means of a suitable qualitative and quantitative selection of the swelling and disintegrating agents, which swell and disintegrate more slowly in the acid regions of the gastrointestinal tract than in regions of higher pH-values, it is possible to delay release of the active compound in the acid regions.

The ionisation conditions in the gastrointestinal tract can be influenced by means of a suitable qualitative and quantitative selection of the fillers.

If the process according to the invention is carried out suitably, particularly by means of a suitable selection of the auxiliary substances, it is possible both to accelerate and to delay the availability of the active compound carbochromene hydrochloride in comparison with the form commercially available hitherto, soft gelatin capsules.

Forms for administration which have an accelerated release of the active compound can be obtained if melting aids having predominantly hydrophilic properties, for example polyethylene glycols, are used and/or colloiddally dispersed silicic acid or amorphous silica is used as the flowing and release agent and/or starch (rice starch, maize starch, potato starch and the like), sodium amylopectin glycollate, sodium carboxymethyl starch or crosslinked polyvinylpyrrolidone is used as the swelling and disintegrating agent.

Forms for administration which have delayed release of the active compound can be obtained if melting aids with predominantly lipophilic properties, for example montan wax acids, montan wax acid esters, carnauba wax or glyceryl mono/di/tristearate/palmitate are used and/or colloiddally dispersed hydrophobic silica is used as the flowing and loosening agent and/or a sodium carboxymethylcellulose, methylcellulose, methylhydroxyethylcellulose or hydroxypropylmethylcellulose is used as the swelling and disintegrating agent.

The resorption of the active compound in

the various sections of the gastro-intestinal tract can be controlled by means of the possibilities indicated.

The granules containing carbochromene hydrochloride which have been manufactured and compounded in accordance with the invention, mixtures thereof and the forms for administration prepared from them have the advantage, compared with the products prepared by processes available hitherto, that the unpleasant properties which arise when carbochromene hydrochloride acts externally, have disappeared to the extent that processing becomes possible without special precautionary measures.

In contrast to the customary methods of manufacture involving dry granulation and moist granulation with subsequent drying, evolution of dust can be largely avoided, especially if the granules are, if appropriate, broken down or classified while still in a plastic state.

In the preparations produced in accordance with the invention, the active compound carbochromene hydrochloride is, surprisingly, also protected against hydrolytic decomposition caused by moisture and heat, so that preparations for the tropics can be packed in normal tropical packings.

#### Example 1.

Carbochromene hydrochloride 1,500 kg,  
polyethylene glycol 6,000 0.332 kg,  
HOECHST Wax E 0.168 kg,  
calcium hydrogen phosphate 0.140 kg,  
Aerosil 200 0.066 kg,  
and  
methylhydroxyethylcellulose 1,000 cP 0.066 kg,

in a high-speed, closed mixer (HENSCHEL FM 10 L FLUID-Mixer equipped with a single-level exchangeable implement), were heated by mixing at 3,600 revolutions/minute, as a result of the friction produced, until granules of approx. 0.5—2 mm particle size were formed at approx. +70°C. While cooling, the granules were broken down on a vibratory sieve machine while in the phase in which they were still plastic.

0.082 kg of sodium amylopectin glycollate, 0.008 kg of Aerosil 200 and 0.038 kg of magnesium stearate were admixed with the cooled granules. This mixture was put into hard gelatin capsules or pressed into tablets or cores for film-coated tablets or dragées.

The dissolution characteristics *in vitro* (SARTORIUS model dissolver; "Sartorius" is a registered Trade Mark) for 1 hard gelatin capsule containing 150 mg of carbochromene hydrochloride and for 1 dragée containing 150 mg of carbochromene hydrochloride are shown in Table 2 compared with the soft gelatin capsules hitherto customary.

The stability under tropical conditions is

shown in Table 1, compared with the forms for administration hitherto customary.

#### Example 2.

Carbochromene hydrochloride 450 g,  
HOECHST Wax E 150 g,  
calcium hydrogen phosphate 130 g,  
hydrogenated castor oil 50 g,  
Aerosil 200 5 g,  
and  
methylhydroxyethylcellulose 1,000 cP 5 g,

were mixed in a slow-speed forced-flow mixer with a heated jacket (a MG 5 LÖDIGE mixer/jacket temperature approx. +90°C) until granules of particle size 0.5—2 mm were formed.

While cooling, the granules were broken down on an oscillating sieve. 10 g of magnesium stearate were admixed and oblong tablets with a weight of 800 mg were pressed and coated with a rapidly soluble aromatised film lacquer.

The dissolution characteristics *in vitro* (SARTORIUS model dissolver) for 1 film tablet containing 450 mg of carbochromene hydrochloride is shown in Table 2, compared with the soft gelatin capsules hitherto customary.

The stability under tropical conditions is shown in Table 1, compared with the forms for administration hitherto customary.

#### Example 3.

Carbochromene hydrochloride 9.000 kg,  
Hoechst Wax E 3.667 kg,  
calcium hydrogen phosphate 2.500 kg,  
polyethylene glycol 6,000 0.333 kg,  
Aerosil 200 0.100 kg,  
and  
sodium carboxymethylcellulose 1,000 cP 0.100 kg,

in a high-speed, closed mixer (HENSCHEL FM 75 L FLUID-Mixer equipped with a two-level exchangeable implement), were heated by mixing, as a result of the friction produced, until granules of approx. 0.5—2 mm particle size were formed at approx. +70°C. While cooling, the granules were broken down on a vibrating sieve.

0.100 kg of Aerosil 200 and 0.200 kg of magnesium stearate were admixed with the cooled granules and oblong tablets with a weight of 800 mg were pressed and coated with a rapidly soluble aromatised-lacquer film.

The dissolution characteristics *in vitro* (SARTORIUS model dissolver) for 1 film tablet containing 450 mg of carbochromene hydrochloride is shown in Table 2.

## Example 4.

	Carbochromene hydrochloride	750.0 g,
	Nifenalol HCl	500.0 g,
	Hydroxycin 2 HCl	50.0 g,
5	polyethylene glycol 6,000	250.0 g,
	HOECHST Wax E	125.0 g,
	calcium hydrogen phosphate	75.0 g,
	Aerosil 200	50.0 g,
		and
10	methylhydroxyethylcellulose	50.0 g,
	1,000 cP	

15 were mixed in a slow-running closed planetary mixer equipped with wipers and a heated jacket (MULTIHOMO MH 10 C/jacket temperature approx. +90°C) until granules of approx. 0.5—2 mm particle size were formed with the charge at approx. 70°C.

20 While cooling, the granules were broken down on a vibrating sieve. 54.0 g of maize starch, 25.0 g of Aerosil 200, 8.5 g of sodium amylopectin glycollate and 62.5 g of magnesium stearate were admixed and the product was pressed into dragée cores.

## Example 5.

25 The homogeneous mixture resulting from grinding 0.050 kg of digoxin with 0.950 kg of calcium hydrogen phosphate was mixed with

	polyethylene glycol 6,000	6.640 kg,
	HOECHST Wax E	3.360 kg,
	calcium hydrogen phosphate	1.800 kg,
30	Aerosil 200	1.320 kg,
		and
	sodium carboxymethylcellulose	1.320 kg,
	1,000 cP	

and with carbochromene hydrochloride 30.000 kg in a slow-running, closed mixer with wipers and a heated jacket (DRAIS FH 165 planetary stirrer/jacket temperature approx. +90°C) until granules of 0.5 to 2 mm particle size were formed.

40 While cooling, the granules were broken down on a vibrating sieve. 1.640 kg of sodium carboxymethyl starch, 0.160 kg of Aerosil 200 and 0.760 kg of magnesium stearate were admixed, and the product was pressed into dragée cores.

## Example 6.

50 The composition and the mode of operation correspond to those of Example 5, but, instead of HOECHST Wax E, equal quantities of carnauba wax or hydrogenated castor oil or glyceryl mono/di/tri-stearate/palmitate were used. The resulting granules, of 0.5—2 mm particle size, were used further without being broken down.

## Example 7.

55 The compositions and modes of operation correspond to those of Examples 1—6, but, instead of calcium hydrogen phosphate, the active compounds digoxin,  $\alpha$ -methyldigoxin and dihydroergotamine tartrate, ground with calcium hydrogen phosphate, were used.

60 The SARTORIUS model dissolver is described in Pharm. Ind., 31 794—799, and Pharm. Ind., 33, 446—454.

TABLE 1

Stability (6 month's storage under tropical conditions, 40°C and 90% relative humidity)

Form for administration	External appearance	% hydrolysis product (acid formed by hydrolysis)
Carbochromene hydrochloride Soft gelatin capsules	spoiled	5—10%
Carbochromene hydrochloride Dragée/alcohol granules	spoiled	5—10%
<hr/>		
Example 1 Dragée	stable	<2%
Example 2 Film tablet	stable	< 2%

TABLE 2  
Release of active compound (SARTORIUS model dissolver)  
(in minutes)

% of active substance released after :

Form for administration	5'	10'	15'	30'	45'	60'	120'	180'	240'	300'	360'
Carbochromene hydrochloride	4	66	99								
Soft gelatin capsules											
Example 1	29	95									
Hard gelatin capsules											
Example 1	4	20	44	81	98						
Dragée											
Example 2				21	28	33	52	66	76	87	96
Film tablets											
Example 3				19	26	32	66	87	98		
Film tablet			11								

WHAT WE CLAIM IS:—

1. Process for the production of a solid preparation containing carbochromene hydrochloride, wherein carbochromene hydrochloride together with, based on the weight of the carbochromene hydrochloride, 1—30% by weight of filler, 1—20% by weight of swelling and disintegrating agent, 1—10% by weight of flowing and loosening agent, and 10—50% by weight of melting aid are submitted to heating and to intermixing, at a temperature in the softening range or melting range of the melting aid, until granules are formed therefrom.

2. Process according to Claim 1, wherein 2—20% by weight of filler are used.

3. Process according to Claim 1 or 2, wherein 2—10% by weight of swelling and disintegrating agent are used.

4. Process according to Claim 1, 2 or 3, wherein 2—8% by weight of flowing and loosening agent are used.

5. Process according to Claim 1, 2, 3 or 4, wherein 15—30% by weight of melting aid are used.

6. Process according to any of Claims 1 to 5, wherein the heating is achieved in a mixer by frictional heat.

7. Process according to any of Claims 1 to 5, wherein the heating is achieved in a mixer by means of a heated surface.
- 5 8. Process according to any of Claims 1 to 7, wherein the agglomerated granules initially formed are broken down.
- 10 9. Process according to any of Claims 1 to 8, wherein 1—15% by weight of flowing and loosening agent and/or mould release agent and lubricant are admixed with the granules.
- 15 10. Process according to any of Claims 1 to 9, wherein 2—10% by weight of flowing and loosening agent and/or mould release agent and lubricant are admixed with the granules.
- 20 11. Process according to any of Claims 1 to 10, wherein a polyethylene glycol is used as the melting aid.
- 25 12. Process according to any of Claims 1 to 11, wherein a colloiddally dispersed or amorphous silicic acid is used as the flowing and loosening agent.
13. Process according to any of Claims 1 to 12, wherein starch, sodium amylopectin glycollate, sodium carboxymethyl starch, or crosslined polyvinylpyrrolidone is used as the swelling and disintegrating agent.
14. Process according to any of Claims 1 to 10, wherein a montan wax acid, a montan wax acid ester, carnauba wax or glyceryl mono/di/tri-stearate/palmitate is used as the melting aid. 30
15. Process according to any of Claims 1 to 10, wherein colloiddally dispersed hydrophobic silicic acid is used as the flowing and loosening agent. 35
16. Process according to any of Claims 1 to 10, wherein a sodium carboxymethylcellulose, methylcellulose, methylhydroxyethylcellulose or hydroxypropylmethylcellulose is used as the swelling and disintegrating agent. 40
17. Process according to claim 1, substantially as described in any of the foregoing Examples.
18. A solid preparation containing carbochrome hydrochloride, produced by a process according to any of the preceding claims. 45

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1976.  
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from  
which copies may be obtained.

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